REMARKS/ARGUMENTS

Initially, Applicant notes that the Office Action dated March 10, 2005 did not include initialed 1449 forms from the information disclosure statements filed June 20, 2002 or April 24, 2003. Applicant submitted duplicate copies of these references at the Examiner's request on February 25, 2005. Applicant received a Notice under 37 CFR 1.251 dated May 20, 2005 in which the Patent Office stated it is reconstructing the IDS filed on June 20, 2002. Applicant has responded to this Notice by submission of the requested documents. The Examiner is requested to provide initialed copies of these latter two 1449 forms with the next Action.

Applicant wishes to thank Examiners Mitchell and Padmanabhan for the courtesy extended to Joe Kentoffio and the undersigned on July 6, 2005 in a personal interview. During the interview, the prior art rejection under 35 U.S.C. § 103 in view of McMahon, Lane, Lilly, and Robertson was discussed. In addition, although the outstanding office action does not cite the McMahon reference directly as showing the use of paroxetine on an as-needed basis, the majority of the discussion in the interview focused on this use of the McMahon reference. In particular, during the course of the interview, the question was discussed whether the McMahon reference discloses that paroxetine is efficacious for treating premature ejaculation on an as-needed basis. This point is discussed in more detail below.

The above-identified patent application has been reviewed in light of the Examiner's Action mailed March 10, 2005. Pursuant to the amendment filed June 2, 2004, Claims 37-42 and 51-54 are pending in the application.

Claim Rejection Under 35 U.S.C. § 103

The Examiner has rejected Claims 37-42 and 51-54 under 35 U.S.C. § 103(a) as being obvious over McMahon, CG and Touma, K *Journal of Urology*, 161(6):1826-30 (1999) (hereinafter "McMahon") and Lane, RM *Journal of Psychopharmacology*, 11(1):72-82 (1997) (hereinafter "Lane") in view of South African Patent Application No. 930694 in the name of Eli Lilly and Company (hereinafter "Lilly") and U.S. Patent No. 5,135,947 (hereinafter "Robertson").

The Examiner argues that McMahon and Lane teach that SSRIs generally can be used to treat premature ejaculation (PE) and that the use of as-needed dosing of a specific

SSRI in the treatment of PE is merely an optimal or workable dosing regimen that could be found by routine experimentation. The Examiner further argues that Robertson teaches that dapoxetine is an SSRI and Eli Lilly teaches the use of dapoxetine for the treatment of PE. Thus, the Examiner asserts that, after reviewing these references, one of skill in the art would have known that dapoxetine is an SSRI and that SSRIs, in general, can be used to successfully treat PE. The Examiner also argues it would therefore be obvious to substitute dapoxetine for the SSRIs used in McMahon and Lane. Furthermore, the Examiner argues, one of skill in the art, having made the substitution of dapoxetine, would have arrived at the use of "as-needed" dosing for the treatment of PE by routine experimentation. Applicant will address the rejection as stated above and in the Office Action. In addition, Applicant will address the issue discussed in the interview of whether the McMahon reference discloses in Study 1 that administration of paroxetine for PE on an as-needed basis in the absence of priming doses is efficacious.

Applicant respectfully disagrees with the rejection for the following reasons:

A) The rejection by the Examiner fails to teach or suggest the step of "administering on an as-needed basis."

The Examiner formulates the rejection by combining a total of four references. The combination of these references does not teach or suggest the claim element of as-needed administration. The Examiner addresses this deficiency by characterizing this claim element as mere optimization. In so doing, the Examiner does not give sufficient weight to this claim element, thereby failing to consider the "invention as a whole," as required by 35 USC § 103(a). Characterizing the element of as-needed administration, which is not taught or suggested by the prior art, as mere optimization is improper for the following reasons.

At the outset, it is important to recognize that PE prevents normal sexual activity. It must also be recognized that sexual activity is often unplanned and spontaneous. Accordingly, effective pharmacological treatment for PE would employ a drug that not only delays ejaculation, but that also can be taken shortly before intercourse without the need for chronic dosing or priming doses, i.e., on an as needed basis.

The Examiner's rejection suggests that the claimed administration on an as-needed basis is only an "optimum or workable range[]" that would be arrived at by

routine experimentation. As-needed dosing of dapoxetine for treatment of PE cannot be considered to be mere optimization of an administration routine. SSRIs are typically used to treat depression and therefore, require chronic administration. Administration of an SSRI on an as-needed basis is a significant departure from the historical understanding of the therapeutic efficacy of SSRIs. In the context of treatment of depression, optimization is done to identify a prolonged therapeutic drug level within a target therapeutic window (where a desired effect is achieved in the absence of adverse effects) that is maintained to establish a desired effect in a patient. In contrast, as-needed dosing represents the use of a drug for a single, immediate effect without regard to establishing and maintaining therapeutic levels in the blood for a long term effect. Under MPEP, 2144.05(II)(B), the parameter of as-needed administration would have to be a recognized result-effective variable in order for as-needed dosing to be optimization through routine experimentation. There was no recognition in the art that dapoxetine could be pharmacologically effective for PE, depression or any other condition on an as-needed basis. Further, there was no recognition that dapoxetine could be pharmacologically effective for PE. Therefore, the use of dapoxetine for treatment of PE on an as-needed basis could not have been a "recognized result-effective" variable. That is, the Applicant is not claiming a specific dosing regimen for a known use of a compound. Rather, the claimed use of dapoxetine for PE is novel by itself and therefore, a specific dosing regimen for that novel use cannot be considering optimization of a known result-effective variable.

Indeed, Applicants have been required by the FDA to perform extensive correctly designed Phase II and Phase III clinical trials that demonstrate administration of dapoxetine to PE patients on an as-needed basis, rather than chronically, is safe and effective. Thus, the use of an SSRI on an as-needed basis for treating PE is not mere optimization of the dosing schedule by routine experimentation as suggested by the Examiner.

Since the as-needed administration of an SSRI, specifically dapoxetine, for treatment of PE cannot be considered to be routine optimization of administration, the rejection made by the Examiner fails to teach or suggest all of the claim limitations of the present invention, and the rejection should be withdrawn.

B) McMahon and Lane do not support the conclusion that SSRIs are generally effective for the treatment of PE.

1) McMahon fails to demonstrate efficacy of paroxetine for the treatment of PE on an as-needed basis.

Initially, Applicants would like to address the Examiner's statement that McMahon teaches that SSRIs generally delay orgasm and reduce sexual excitement thereby having a beneficial effect on premature ejaculation. This statement reflects a misunderstanding of the introductory remarks made by the study's authors. In the passage cited by the Examiner, McMahon is describing the effects of serotonin in the rat model as having an inhibitory effect on sexual function. Therefore, the authors ***postulate***, "serotonin re-uptake inhibitors should reduce sexual excitement and have a beneficial effect on premature ejaculation." (See p. 1826, paragraph 2.) This statement by the authors is merely an initial observation from a rat model that provided the impetus to pursue the small human trial described in McMahon and does not support the assertion that all SSRIs delay orgasm and have a beneficial effect on premature ejaculation in humans. The authors continue in their introductory remarks to cite several additional reports of beneficial effects of chlomipramine (a tricyclic antidepressant), and fluoxetine, sertraline and paroxetine (SSRIs) in treating PE or improving ejaculatory control following ***daily*** administration. None of these reports support the conclusion that SSRIs generally can be used to treat PE on an as-needed basis, but merely provided the authors a basis for their investigation into the use of paroxetine as-needed 3-4 hours before sexual intercourse to treat PE.

Turning to the human studies disclosed by McMahon, neither the design or the results of the studies would lead one of skill in the art to conclude that an SSRI could be used to treat PE patients on an as-needed basis. The design of the McMahon studies are, at best, empirical pilot studies exploring the merits of paroxetine (an SSRI specifically designed to treat conditions pertaining to mood and affect that is administered daily to achieve the desired therapeutic effect) in the treatment of patients with PE. The scientific and methodological issues discussed below bring into question any definitive conclusion on the role of paroxetine for the treatment of PE on an as-needed basis. Therefore, the

Examiner's reliance on McMahon for the broader point that SSRIs generally are effective for treatment of PE is misplaced.

- The McMahon study did not use an appropriate number of men suffering with PE to address the study objective. To do this, a statistical power calculation using standard deviations from other studies and on published literature with a large number of subjects (greater than the 26 and 42 in each of the studies described in McMahon) would be required for scientific validity. Also, no standard deviation values are provided for by McMahon. These major omissions bring the data set from McMahon into serious question.
- The McMahon studies were single-blind studies. It is not possible to make any definitive clinical conclusion as to paroxetine's effect in patients with PE on the basis of such a study because of the subjective nature of PE as a disease. PE is treated with behavioral therapy, not just pharmaceutical therapy. As such, it is important to exclude any role the clinician's behavior toward the patient may have while the patient is participating in a clinical study. This is known in the art as known as "investigator effect." A single-blind study means that the patient is blinded to whether he is taking placebo or drug, but the clinician is not blinded. Thus, the clinician may be biased during the study. Rather, a correct clinical study should be a double blind study in which the clinician is also blinded to whether the patient is receiving drug or placebo, thereby removing all chance of bias. The importance of the difference between a single-blind and double-blind study on the conclusions that can be drawn from that study as well as the effect on perceived research results is described in Day, SJ and Altman, DG Blinding in Clinical Trials and Other Studies, *British Medical Journal*, 321:504 (2000), a copy of which is included here for the Examiner's convenience. The authors of this review point out that, on average, trials that have not used appropriate levels of blinding, such as McMahon, show larger treatment effects than blinded studies.

Thus, after reviewing McMahon, one of skill in the art would conclude that the data presented is merely suggestive and that further, more rigorous clinical studies would need to be performed for a physician to understand the actual efficacy of paroxetine as a treatment for PE.

One of skill in the art would also conclude from the results presented by McMahon, and from McMahon's own interpretation of those results, that a period of pre-loading of paroxetine is needed to obtain an effective response when administered on an as-needed basis. This conclusion is made even in view of comments in the discussion that "paroxetine as needed was significantly better if patients were initially treated with the drug daily." The Examiner relied on such comments as a suggestion that as-needed dosing, with no pre-loading, while not as effective as with pre-loading, is effective to some extent. Such comments by McMahon were made in the context of comparing the results of Study 1 (as-needed use) and Study 2 (having 2 weeks of daily chronic dosing before as-needed use). Such comments cannot be construed as a statement that the results in week 1 of Study 1 were efficacious because such a construction would be contrary to McMahon's statement that the results of week 1 in Study 1 were not statistically significant.

Regarding Study 1, McMahon states that "ejaculatory latency time for groups A and B during treatment with paroxetine as needed was statistically superior to placebo at 2, 3 and 4 weeks ($p<0.001$, table 2, fig. 1)." This statement means, by the authors' admission, that there was no statistically superior increase in ejaculatory latency in the first week. As noted by McMahon, Figure 1 illustrates the point that a significant increase in IELT over placebo did not occur until week 2. These results indicate to one skilled in the art that "1-2 weeks of 'priming doses' of paroxetine are required," as is noted at p. 5, ll. 6-12, of the application. In Study 2, McMahon then daily dosed PE patients with paroxetine for 2 weeks prior to commencing as-needed dosing. McMahon concludes that the "[m]ean ejaculatory latency time was greater during the paroxetine as needed phase of study 2 than that of study 1 ($p<0.05$), suggesting that ejaculatory control achieved with paroxetine as needed is significantly better if patients are initially treated with the drug daily." McMahon reiterates this view of his results when he states that "[p]aroxetine as needed appeared to be more efficacious after initial chronic dosing."

Again, at the conclusion of his article, McMahon states that "[p]aroxetine as needed appears to be more efficacious after an initial period of paroxetine daily." One of skill in the art would conclude from McMahon's studies that paroxetine is not a suitable drug for the treatment of PE because it requires a period of pre-loading. In fact, the lead author of McMahon (obviously aware of the earlier McMahon reference) today states that "[e]ffective, on-demand therapy that is effective within the time frame most suitable for the PE patient . . . is not currently available." (See McMahon, C., J. Sex Med., Supp2:94-5 (2005) a copy of which is included with this response for the Examiner's convenience; paper based on a presentation given by the author at a symposium sponsored by the licensee of the assignee of this application). Further, the article clearly does not support a broader conclusion that SSRIs are generally effective for the treatment of PE, or that the substitution of a given SSRI would provide the same patient responses.

If the Examiner continues to rely on McMahon as disclosing efficacious as-needed dosing of paroxetine in the absence of priming doses for treatment of PE, contrary to McMahon's assertion that there was no statistically significant effect until the second week of use, Applicant requests, pursuant to MPEP 2144.03, that the Examiner either provide some documentary evidence in the next Office Action that it is proper to rely on data that is not statistically significant (i.e., McMahon's Study 1, week 1 data) or provide an Examiner's affidavit pursuant to 37 CFR 1.104(d)(2) to that effect. If the Examiner contends that he is not required to do either, Applicant reserves the right to submit a declaration of a person skilled in this art supporting Applicant's position that data that is not statistically significant would not be relied upon by one skilled in the art.

Being effective for treatment of PE on an as-needed basis without priming doses is a significant advantage of the use of dapoxetine, as claimed. For instance, if paroxetine is used by a patient in a first instance there will be no benefit (as shown in week 1 of Study 1 of McMahon). If that patient does not use paroxetine again for a month (greater than the washout period in Study 1), the patient will again not see any benefit because the drug from the first administration will have been cleared from the patient's body, making the second administration, in effect, a "first" dose. In contrast, as shown by Table 12 of the present application, dapoxetine can be used to effectively treat PE on an as-needed basis without priming doses because it can provide statistically significant benefit from

the first dose. Therefore, even in instances in which there are long time periods between use for a patient, that patient will still obtain a benefit from the first administration of dapoxetine.

2) Lane only discloses inapplicable preliminary studies and initial case reports.

The Examiner states that Lane also teaches the use of SSRIs in general for the treatment of premature ejaculation and specifically, that low dosages of SSRIs, administered on an as-needed basis prior to intercourse are efficacious in the treatment of premature ejaculation. Applicants disagree.

Lane presents a review of the sexual dysfunctions caused by SSRIs as well as possible methods of managing these adverse effects. After reviewing the myriad of sexual dysfunctions associated with these drugs, the author includes a review of "a number of uncontrolled trials of serotonergic drugs" that have indicated "potential efficacy" in the management of premature ejaculation. (See p. 79, first full paragraph) The preliminary studies reviewed include a trial of the tricyclic antidepressant clomipramine and two SSRIs; sertraline and paroxetine. (See p. 79, second full paragraph) The paroxetine study reviewed included titration of the paroxetine dose to 40mg/day (double the normal daily adult dose) for five weeks. The sertraline study reviewed in Lane included doses of up to 200mg/day for over three weeks (quadruple the normal daily adult dose). From these two studies the author concluded: "[t]he placebo-controlled studies with sertraline and paroxetine used high doses. The efficacy of lower doses and different dosing regimens has yet to be fully explored." Thus, Lane questions the applicability of these two initial reports to the clinical use of sertraline and paroxetine themselves and certainly does not support the general efficacy of SSRIs in the treatment of PE.

Lane also includes a review of a study by Swartz using more typical adult dosing of sertraline (25-50mg/day) on an as-needed and on a "regular dosing" basis finding that ejaculatory latency of the combined patient populations increased to an average of twenty minutes – about a four-fold increase over the previous high dose sertraline study. (See p. 79, fourth paragraph) Although Lane states that these observations were collected from three patients (as needed) and seven patients (regular dosing) in an "open study," it is unclear from the original abstract that any of the patients were actually treated "as-

needed."[1] Moreover, the seemingly amazing results, that are inconsistent with any results available at that time, or that have been published subsequent to that report, appear to have been an average of both daily and as-needed dosing. Further, the Swartz abstract notes that the "26-hour elimination half life [of sertraline] allows considerable liberties in dosing schedules." This is obviously a preliminary case report and, even in combination with the high dose studies of paroxetine and sertraline, one of skill in the art clearly would not regard this report as supporting that all SSRIs, administered in low doses on an as-needed basis prior to intercourse, would be efficacious in treating PE.

C) The rejection under 35 U.S.C. § 103(a) McMahon, Lane, Lilly and Robertson is based on an "obvious to try" standard.

Both the data presented in McMahon and the initial reports reviewed in Lane, taken separately or together, indicate that, at the time of filing the instant application, there was only preliminary evidence suggesting that paroxetine and sertraline (as well as the tricyclic clomipramine) prolong time to ejaculation and that this adverse effect might be exploited clinically in the treatment of PE. Importantly, the report of as-needed use of sertraline is unclear whether as-needed dosing was even used and in any event, the report notes that as-needed dosing is not really a concern for sertraline since it has a 26 hour half life, allowing "considerable liberties" in dosing. In addition, even today, the lead author of McMahon states that "[e]ffective, on-demand therapy . . . is not currently available." Therefore, the suggestion made by the Examiner that one skilled in the art, based on the cited references, would turn to the use of dapoxetine on an as-needed basis to treat PE with a reasonable expectation of success is not supported because at the time of filing, no SSRIs had been shown to be effective for treating PE on an as-needed basis. At best, the references cited by the Examiner at best would have made it "obvious to try" dapoxetine, or any SSRI, under different dosing regimens, in the treatment of premature ejaculation in order to produce the presently claimed invention.

The Federal Circuit has provided clear direction with respect to arguments based on an "obvious to try" theory. The court has held that an "obvious to try" situation exists

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[1] Swartz states that "[t]wo patients required a daily dose of 50 mg. Three patients remained on a 25 mg. dose on a regular daily schedule. Five patients remained on a 25mg/day dose taken on an 'as needed' schedule."

when a general disclosure may pique a scientist's curiosity, such that further investigation might be done as the result of a disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. In re Eli Lilly & Co., 14 USPQ 2d 1741, 1743 (Fed.Cir. 1990). The court held, however, that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103. See Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ 2d 1923, 1928 (Fed.Cir. 1990). The preliminary studies presented in McMahon and Lane may indicate to one of skill in the art that there is a potential clinical use of paroxetine and sertraline in the treatment of PE that could be explored further but clearly do not rise to the level of making it obvious that SSRIs, as a class, are generally effective in the treatment of PE.

While the prior art clearly indicates that SSRIs generally can cause sexual dysfunction and there was a suggestion that certain SSRIs might be useful for treating PE, there was no guidance that specific SSRIs were useful, nor any guidance in the art as to how to select SSRIs that would be useful. Indeed, as noted above, the mechanism of action by which drugs from many different classes prolong ejaculation remains unknown. Thus, the skilled person would have no basis on which to identify drug candidates and would be left with empirically testing SSRIs to look for useful compounds.

In this regard, the Examiner cited Lilly for the proposition that Lilly teaches the use of dapoxetine for the treatment of PE. As discussed in more detail below, Lilly does not. Lilly merely includes dapoxetine in a laundry list of SSRIs and identifies a vast listing of conditions with which such compounds might be useful. Moreover, no data or experimental basis is provided that any of the compounds could be used with any of the conditions. Thus, the skilled person would interpret this reference as no more than an invitation to experiment.

The McMahon and Lane references also indicate that no consistently-effective dose or frequency had been established for any of the drugs reviewed. The references also indicate that no well conducted, randomized, double blind, parallel group, placebo controlled studies had been conducted for any of these drugs having sufficient statistical power from which to draw dosing guidelines or definitive conclusions of efficacy. Therefore, the assertion that one of skill in the art, at the time of filing of the instant

application, would have reviewed the teachings of McMahon and Lane and concluded that SSRIs were generally effective in treating PE and that SSRIs administered on an as-needed basis prior to intercourse are effective in treating PE is clearly incorrect. Indeed, both the McMahon reference and the McMahon (2005) article support the contrary conclusion. The McMahon reference repeatedly states that ejaculatory control achieved with paroxetine as needed is significantly better if patients are initially treated with the drug daily (Abstract; p. 1827, col. 2, ll. 45-48; p. 1828, col. 2, ll. 36-39; p. 1830, col. 1, ll. 1-2). Moreover, the McMahon reference recognizes that as needed administration of paroxetine is not immediately effective and prolonged ejaculatory control is seen within the first two weeks. (p. 1828, col. 2, ll. 30-32) The McMahon reference further states "[p]aroxetine as needed appeared to be more efficacious after initial chronic dosing." (p. 1829, col. 1, ll. 33-34). These reservations expressed in McMahon about the efficacy of as-needed dosing of paroxetine for PE are echoed even today by the lead author in the McMahon (2005) article, who states that at this time [2005], there is still no SSRI that has gained regulatory approval for the treatment of PE, and that "[e]ffective, on-demand therapy that is effective within the time frame most suitable for the PE patient . . . is not currently available." Thus, the author of the McMahon reference cited by the Examiner disavows the notion that, even today, any of the available SSRIs are effective on an as-needed basis in treating PE.

D) Eli Lilly does not teach the use of dapoxetine for the treatment of PE

South African Patent Application No. 930694 (Eli Lilly) discloses dapoxetine, along with fluoxetine/lovan, duloxetine, amersergide, 228729 and zatosetron, and identifies the potential use of these compounds for treatment of hundreds of conditions spanning eight pages of single-spaced type, including conditions in such disparate areas as tobacco withdrawal, premenstrual conditions, weight loss, memory loss, circadian rhythm disorders, fatigability, sexual disorders (including premature ejaculation), psychoses, nonspecific complaints, and so on. This disclosure is so broad and general as to not effectively disclose the use of dapoxetine for premature ejaculation. Even if this South African application is construed to effectively disclose the use of dapoxetine for

premature ejaculation, there is no disclosure or suggestion of the use of dapoxetine on an as-needed basis or the characteristic that it is effective in the absence of priming doses.

The Examiner has stated that these observations regarding the teachings (or lack thereof) of Eli Lilly are not indicative of nonobviousness as the Examiner is relying on McMahon, Lane and Robertson and nonobviousness cannot be shown by attacking a reference individually. However, the Examiner has cited Eli Lilly for the proposition that the reference teaches the treatment of PE with the instantly claimed compounds, and Applicant's comments address this proposition. Applicant submits that Eli Lilly does not effectively disclose the use of dapoxetine for PE and therefore does not overcome the shortcomings of McMahon and Lane in failing to teach the use of dapoxetine for the treatment of PE. Additionally, Eli Lilly does not disclose or suggest that dapoxetine is useful on an as-needed basis or that as-needed dosing could be achieved by routine experimentation.

In conclusion, Applicant submits that the Examiner's rejection of Claims 37-42 and 51-54 as obvious in light of McMahon, Lane, Eli Lilly and Robertson should be withdrawn as McMahon and Lane did not, at the time of filing the instant application, establish that SSRIs are generally useful for the treatment of PE, nor did Eli Lilly establish that dapoxetine was effective in the treatment of PE. Furthermore, establishing the efficacy of a drug in treating a disorder on an as-needed basis requires more than routine experimentation. Therefore, the combined teachings of these references would not have taught one of skill in the art that dapoxetine would be effective for the treatment of PE on an as-needed basis as recited in Claims 37-42 and 51-54.

Based upon the foregoing, Applicant believes that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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